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TRANSMITTAL OF PRIORITY DOCUMENT UNDER 35 USC §119

Applicants hereby confirm their claim of priority under 35 USC § 119 from the following application(s):

Sweden Application No. 0003810-9 filed October 20, 2000.

A certified copy of the application from which priority is claimed is submitted herewith.

Please apply any charges to Deposit Account No. 06-1050, referencing 13425-052001.

Respectfully submitted,

Date: February 27, 2002

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NOVEL COMPOUNDS, THEIR USE AND PREPARATION

FIELD OF INVENTION

The present invention relates to novel 3-, 4- or 5-substituted-N1-(benzensulfonyl)indoles compounds, to pharmaceutical compositions comprising the compounds and to the use of the compounds for the preparation of a medicament for the treatment of obesity and CNS disorders as well as method of treatment of these disorders.

BACKGROUND OF INVENTION

Obesity is a condition characterized in an increase in body fat content resulting in excess body weight above accepted norms. Obesity is the most important nutritional disorder in the western world and represents a major health problem in all industrialized countries. This disorder leads to increased mortality due to increased incidences of diseases such as cardiovascular disease, digestive disease, respiratory disease, cancer and NIDDM (type II diabetes). Searching for compounds, which reduce body weight has been going on for many decades. One line of research has been activation of serotonergic systems, either by direct activation of serotonin receptor subtypes or by inhibiting serotonin reuptake. The exact receptor subtype profile required is however not known.

Serotonin (5-hydroxytryptamine or 5-HT), a key transmitter of the peripheral and central nervous system, modulate a wide range of physiological and pathological functions, including anxiety, sleep regulation, aggression, feeding and depression. Multiple serotonin receptor subtypes have been identified and cloned. One of these, the 5-HT_6 receptor, was cloned by several groups in 1993 (M Ruat, E Traiffort, J-M Arrang, J Tardivel-Lacombe, J Diaz, R Leurs, J-C Shwartz. *Biochem. Biophys. Res. Commun.* 1993, 193 (1) 268-276; M Sebben, H Ansanay, J Bockaert, A Dumuis, *NeuroReport* 5, 2553-2557 (1994).) This receptor is positively coupled to adenylyl cyclase and displays affinity for antidepressants such as clozapine. Recently, the effect of 5-HT_6 antagonist and 5-HT_6 antisense oligonucleotides to reduce food intake in rats has been reported (JC Bentley, CA Mardsen, AJ Sleight and KC Fone Effect of 5-HT_6 antagonist Ro 04-6790 on food consumption in rats traineds to a fixed feeding regime *Br J Pharmac.* 1999 Suppl 126 P66; JC Bentley, AJ Sleight, CA Mardsen, KCF

Fone 5-HT_6 antisense oligonucleotide ICV affects rat performance in the water maze and feeding *J Psychopharmacol Suppl* A64 1997 255).

Compounds with enhanced affinity and selectivity for the 5-HT_6 receptor have been identified, e.g in WO 00/34242 and by M. Isaac, A. Slassi; T. Xin, N. MacLean, J. Wilson, K. McCallum, H. Wang and L. Demchyshyn: 6-Bicyclopiperazinyl-1-arylsulfonylindoles and 6-Bicyclopiperidinyl-1-arylsulfonylindoles derivatives as novel, potent and selective 5-HT_6 receptor antagonists; *Bioorganic & Medicinal Chemistry Letters* 10 (2000) 1719-1721.

OBJECT OF INVENTION

It is an object of the present invention to provide new compounds with affinity for the 5-HT_6 receptor.

It is a further object of the invention to present compounds for use in therapy of a mammal including human being.

A further object of the invention is use of compounds for the manufacture of a medicament for treating or preventing a disease related to the 5-HT_6 receptor.

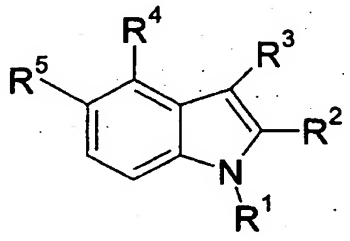
Yet another object of the invention is a pharmaceutical composition comprising compounds with affinity for the 5-HT_6 receptor as an active ingredient.

Finally, an object of the invention is a method of treatment or prophylaxis of a disease related to the 5-HT_6 receptor.

SUMMARY OF THE INVENTION

The objects of the invention are achieved by the compounds, the use of the compounds and method of treatments as claimed in the claims.

According to the invention a compound of the general formula (I) is provided:



(I)

in which

R^1 is – SO_2-Ar; -SO_2-alkyl,

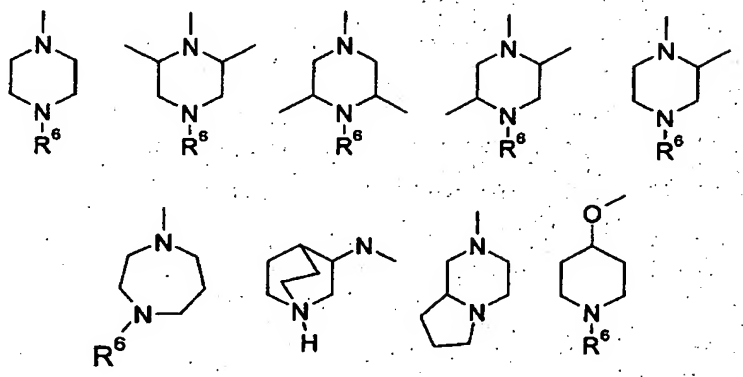
and Ar = phenyl, optionally substituted with F, Cl, Br, C_{1-6} alkyl, CF_3, hydroxy, C_{1-6} alkoxy, OCF_3, amino, alkylamino, dialkylamino, NO_2, methylcarboxyl, aminocarbonyl, SR^7 where R^7 is hydrogen or C_{1-6} alkyl; 1-naphthyl, 2- naphthyl; a bicyclic heterocyclic ring or a 5 to 7-membered partially or completely saturated heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur; and

alkyl = linear or branched C_{1-6} alkyl;

R^2 = H, linear or branched C_{1-4} alkyl;

R^3 = H, 3-[1-azabicyclo[2.2.2]oct-2-en]yl, 3-quinuclidinyl;

R^4 = H, or the following amine groups:



in which R^6 = H or a linear or branched C_{1-6} alkyl group;

R^5 = R^4 or H, hydroxy, C_{1-3}alkoxy, F, NO_2, CF_3, OCF_3;

and pharmaceutically acceptable salts, hydrates, stereo isomeric forms thereof including diastereomers and enantiomers and racemates.

The invention also relates to the compounds of the general formula (I) for use in therapy of a mammal including human being.

In another aspect, the invention relates to use of the compounds of the general formula (I) for the manufacture of a medicament for treating or preventing a disease related to the serotonin related 5-HT_6 receptor.

In yet another aspect the invention relates to a pharmaceutical composition comprising a compound of the general formula (I) as an active ingredient together with pharmacologically and pharmaceutically acceptable carriers.

Finally the invention provides a method of treatment or prophylaxis of a disease related to the serotonin related 5-HT_6 receptor in mammals including human beings.

The method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of the general formula (I).

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention it has been found that the compounds of formula (I) show affinity for the 5-HT_6 receptor as antagonists at a low nano molar range. The 5-HT_6 antagonist compounds of the present invention are useful for treating or prophylaxis of obesity and for the treatment or prophylaxis of memory and CNS disorders such as Schizophrenia and Parkinson's disease and depression.

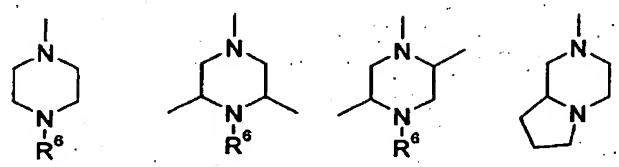
Preferred compounds of the invention are compounds in which in the general formula (I)

R^1 = $-SO_2$-Ar in which

Ar = phenyl substituted with F or C_{1-6}-alkyl; 1-naphthyl, 2-naphthyl;

R^2 = H, propyl;

R^4 =



R^6 = H

R^5 = H or C_{1-3} alkoxy.

The following compounds are particularly preferred embodiments of the invention:

1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,

1-[(4-fluorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole,

1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole,

3-(1-azabicyclo[2.2.2]oct-2-en-3-yl)-1-(phenylsulfonyl)-1H-indole,

5-methoxy-1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,

4-(4-ethyl-1-piperazinyl)-1-(phenylsulfonyl)-1H-indole,

1-[(4-methylphenyl)sulfonyl]-4-(4-methyl-1-piperazinyl)-1H-indole,

1-(phenylsulfonyl)-5-(1-piperazinyl)-1H-indole,

4-(2,5-dimethyl-1-piperazinyl)-1-(phenylsulfonyl)-1H-indole,
4-(2,6-dimethyl-1-piperazinyl)-1-(phenylsulfonyl)-1H-indole,
4-(1,4-diazepan-1-yl)-1-(phenylsulfonyl)-1H-indole,
2-[1-(phenylsulfonyl)-1H-indol-4-yl]octahydropyrrolo[1,2-a]pyrazine1-(2-naphthylsulfonyl)-4-(1-piperazinyl)-1H-indole,
1-(1-naphthylsulfonyl)-4-(1-piperazinyl)-1H-indole,
1-[(4-methylphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole,
N-(1-azabicyclo[2.2.2]oct-3-yl)-N-{1-[(4-methylphenyl)sulfonyl]-1H-indol-4-yl}amine,
2-ethyl-4-(4-ethyl-1-piperazinyl)-1-[(phenyl)sulfonyl]-1H-indole,
2-ethyl-1-(4-methyl-phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,
4-(2,5-dimethyl-1-piperazinyl)-2-ethyl-1-(phenylsulfonyl)-1H-indole,
4-(2,5-dimethyl-1-piperazinyl)-1-[(4-methylphenyl)sulfonyl]-2-propyl-1H-indole,
4-(4-ethyl-1-piperazinyl)-1-[(4-methylphenyl)sulfonyl]-2-propyl-1H-indole,
4-(4-ethyl-1-piperazinyl)-5-fluoro-1-[(4-methylphenyl)sulfonyl]-1H-indole,
5-fluoro-4-(1-piperazinyl)-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1H-indole,
5-chloro-1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,
5-chloro-1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,
1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-5-methoxy-4-(1-piperazinyl)-1H-indole,
1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-5-(1-piperazinyl)-1H-indole,
1-[(4-methylphenyl)sulfonyl]-4-(3-methyl-1-piperazinyl)-1H-indole,
1-[(4-methylphenyl)sulfonyl]-4-(4-piperidinyloxy)-1H-indole,
1-[(4-methylphenyl)sulfonyl]-4-(3-methyl-1-piperazinyl)-1H-indole.

Most preferred embodiments of the invention are the compounds 1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,
1-[(4-fluorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole and
1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole.

Certain compounds of formula (I) are capable of existing in stereo isomeric forms including diastereomers and enantiomers and the invention extends to each of these stereo isomeric forms and to mixtures thereof including racemates. The different stereo isomeric forms may be separated from each other by conventional methods. Any given

isomer may be obtained by stereo specific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

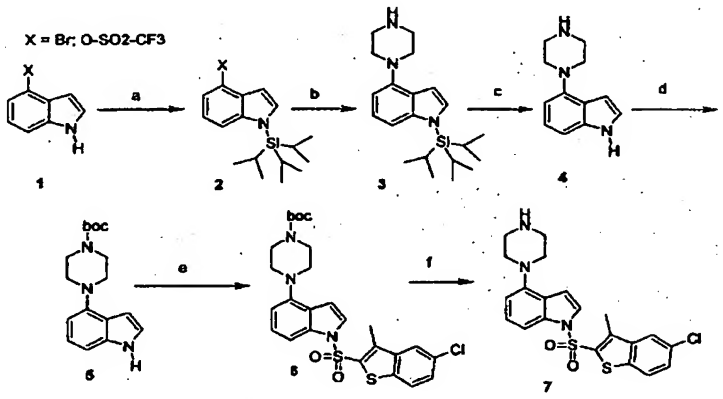
The compounds of the formula (I) can form acid addition salts with acids such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulfonic.

Compounds of formula (I) may also form solvates such as hydrates and the invention also extends to these forms. When referred to herein, it is understood that the term "compound of formula (I) " also includes these forms.

The compounds according to the invention may be prepared according to known or analogue methods or following the procedure described below in Schemes 1 and 2.

General synthetic schemes

Scheme 1:



(a) NaH, TIPS-Cl (tri-isopropyl-silyl chloride), DMF (dimethyl formamide), 0 °C

(b) Piperazine, NaOt-Bu (Natrium tert-butoxide), $Pd(OAc)_2$ (Palladium acetate), *t*-Bu_3P (tert-tributylphosphine), xylene, 120 °C

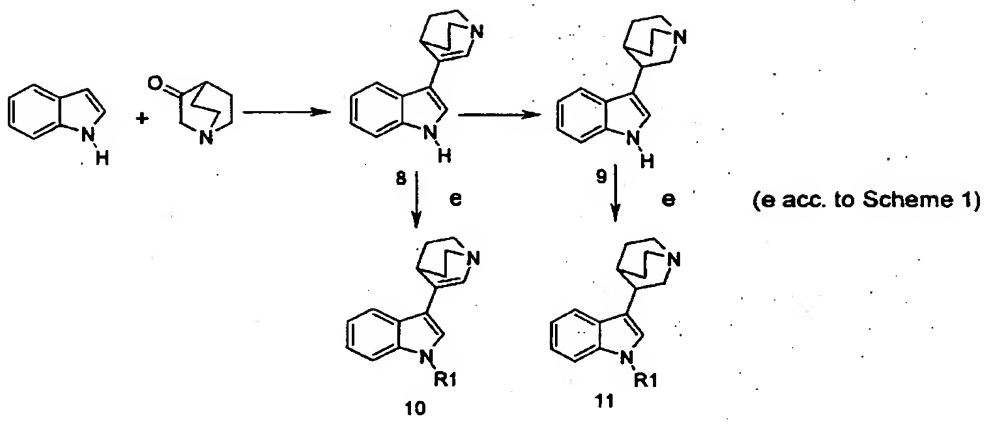
(c) TBAF (tetrabutylammonium fluoride), THF (tetrahydrofurane)

(d) $(BOC)_2O$ (di-tert-butyl dicarbonate), Et_3N, DIMAP (dimethylaminopyridine), DMF

(e) NaH, Aryl-SO_2Cl, DMF

(f) Ether, methanol and HCl gas

Scheme 2:



Synthesis according to Scheme 1:

General procedure for the preparation of intermediate type 2:

5-Br-indole was dissolved in dry DMF. The solution was cooled (0 °C) and NaH (1.3 eq) was added in portions. The suspension was stirred for 1h at 0 °C followed by the addition of tri-isopropyl-silyl chloride (1.2 eq). The reaction was stirred for 6 h, quenched with $NaHCO_3$. The volatile compounds were evaporated and the organic material was extracted with DCM. The organic phase was washed with water, dried ($MgSO_4$), filtered and concentrated to give the crude mixture. The crude mixtures were purified by chromatography as a general method (hexane:ethylacetate 9:1).

General procedure for the preparation of intermediate type 3

The protected indoles are coupled with diamines of different type by using the Buchwald palladium catalyzed reaction.

$Pd(OAc)_2$ (0.02 eq), *t*-Bu_3P (0.04 eq) and Na*t*-BuO (10 eq) were suspended in xylene. Diamine dissolved in xylene was added to the suspension via a syringe. The mixture was heated at 80 °C for 10 minutes followed by the addition of the intermediate type 2 dissolved in xylene. The reaction was left at 80 °C for 1h. The volatile compounds were evaporated and the crude was purified on a silica column to give the desired products.

General procedure for the preparation of intermediate type 4:

The silyl protecting group was removed by treatment with tetrabutyl ammonium fluorine in THF.

General procedure for the BOC protection of the diamino group (preparation of intermediate type 5) specifically synthesis of tert-butyl 4-(1H-indol-4-yl)-1-piperazinecarboxylate:

4-Piperazinoindole (1eq), DMAP (0.1 eq) and Et_3N (4 eq) were dissolved in DMF and stirred at room temperature. $(BOC)_2O$ (1.1 eq) was added and the reaction was stirred at room temperature (12 h). DMF was evaporated and the residue was purified by silica column mixture of chloroform, methanol and ammonia were used as eluent. HPLC 100 % purity, (M+) 302.2.

General procedure for the preparation of intermediate type (6) specifically synthesis of tert-butyl 4-{1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-1H-indol-4-yl}-1-piperazinecarboxylate

The intermediate 5 (1.0 eq) was dissolved in DMF and NaH (1.3 eq) was added and the suspension was stirred for 0.5 h under nitrogen atomosphere. 5-Chloro-3-methylbenzo[B]thiophene-2-sulfonylchloride (1.2 eq) was added and the reaction was stirred overnight at room temperature. The volatile compounds were evaporated and the residue was dissolved in DCM, washed with a saturated solution of $NaHCO_3$ and dried ($MgSO_4$), filtered and concentrated to give an oily residue that was purified on silica column using mixtures of hexane and ethylacetate (7:3) as eluent to tert-butyl 4-{1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-1H-indol-4-yl}-1-piperazinecarboxylate HPLC 100 %, 1H-NMR (d-$CDCl_3$) δ 1.5 (s, 9H), 2.6 (s, 3H), 3.0 (m, 4H), 3.6 (m, 4H), 6.8-7.8 (m, 8 H Arom).

General procedure for the removal of the BOC protecting group for the preparation of intermediates type 7:

The BOC groups for the intermediates 6 are removed by dissolving the compound in methanol followed by addition of ether saturated with HCl gas. The salts are filtered and dried.

Synthesis according to Scheme 2:

Synthesis of 3-(1-azabicyclo[2.2.2]oct-2-en-3-yl)-1H-indole (8)

Indole (1 eq) and 3-quinuclidinone (1 eq) in methanol were heated at reflux temperature for 48 h. The methanol was evaporated and the residue was purified by silica column. Methanol (15 %) and a THF mixture were used as eluent. The purification yielded 31% of the final compound.

Synthesis of 3-(1-azabicyclo[2.2.2]oct-3-yl)-1H-indole (9)

The compound was obtained by reduction of **8** with $NaBH_4$ in THF with addition of BF_3-Et_2O. The reaction is quenched with HCl in ethanol.

The compounds according to formula (I) can conveniently be administered in a pharmaceutical composition containing the compound in combination with pharmacologically and pharmaceutically acceptable carriers. Such pharmaceutical compositions can be prepared by methods and contain carriers or excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975). The compounds and compositions can be administered orally, parenterally (for example, by intravenous, intraperitoneal or intramuscular injection), topically, or rectally.

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such

as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The compounds or compositions can also be administered intravenously, or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils.

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The compound can be administered in unit dosage form; for example, containing about 0.05 mg to about 500 mg, conveniently about 0.1 mg to about 250 mg, most conveniently, about 1 mg to about 150 mg of active ingredient per unit dosage form. The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals.

The compositions can be administered orally, sublingually, transdermally, or parenterally at dose levels of about 0.01 to about 150 mg/kg, preferably about 0.1 to about 50 mg/kg, and more preferably about 0.1 to about 30 mg/kg of mammal body weight.

The invention will now be further illustrated with the following non-limiting examples:

Example 1:

1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole hydrochloride was prepared according the methods stated in Scheme 1 above starting from commercially available 4-piperazinoindole (4 in Scheme 1) that undergoes the procedures described for steps d-f in Scheme 1 to afford 1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole hydrochloride (yield 80%). HPLC purity >95%; 1H NMR (DMSO-*d6*) δ 9.64 (br s, 2 H), 8.00-7.85 (m, 3 H), 7.79 (d, J = 3.77 Hz, 1 H), 7.70-7.65 (m, 1 H), 7.63-7.60 (m, 3 H), 7.27-7.22 (m, 1 H), 6.95 (d, J = 3.76 Hz, 1 H), 6.81-6.77 (m, 1 H), 3.30-3.20 (m, 4 H); 13C NMR

(DMSO-*d6*) δ 144.79, 137.02, 135.22, 134.62, 129.82, 126.85, 125.63, 125.54, 123.49, 111.15, 107.87, 107.76, 47.81, 42.86; MS (posES-FIA) m/z 342 (M+H).

Example 2:

1-[(4-fluorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride was prepared in the same manner as in Example 1, starting from commercially available 4-piperazinoindole that undergoes procedures described for steps d-f in Scheme 1 to afford 1-[(4-fluorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride (yield 70%), HPLC purity >95%; 1H NMR (DMSO-*d6*) δ 3.26 (bs, 8H), 6.80 (bs, 1H), 6.95 (bs, 1H), 7.26 (bs, 1H), 7.61 (app t, 2H), 7.80 (bs, 1H), 8.06 (bs, 1H), 9.30 (bs, 1H); 13C NMR (DMSO-*d6*) δ 165.20, 144.94, 135.14, 133.31, 130.06 (2C), 125.62 (2C), 123.50, 117.25, 117.06, 111.15, 107.92, 107.71, 47.82 (2C), 42.98 (2C); MS (posES-FIA) m/z 360 (M+H).

Example 3:

1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride was prepared in the same manner as in Example 1 starting from commercially available 4-piperazinoindole that undergoes procedures described for steps d-f to afford 1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride (yield 45%), HPLC purity >95%; MS (posES-FIA) m/z 446 (M+H)). 13C NMR (DMSO-*d6*) δ 145.05, 139.82, 139.35, 137.46, 135.14, 133.31, 130.96, 128.70 (2C), 125.62, 124.89, 124.12, 123.52, 111.42, 107.91, 107.71, 47.87 (2C), 43.03 (2C), 12.27; 1H NMR (DMSO-*d6*) δ 2.65 (s, 3H), 3.26 (bs, 8H), 6.82 (app d, 1H), 7.00 (appd, 1H), 7.28 (app t, 1H), 7.60 (app dd, 2H), 7.87 (app d, 1H), 8.08-8.12 (m, 2H).

In the examples the structure of the prepared compounds were confirmed by standard spectroscopical methods and elemental analysis and/or high resolution MS. The NMR data were obtained on a JEOL JNM-EX 270, a Bruker 400 DPX or a Bruker DRX 500 spectrometer. IR spectra were obtained on a Perkin Elmer SPECTRUM 1000 FT-IR spectrometer. High resolution MS were obtained on a Micromass LCT spectrometer. Elemental analysis was performed by Mikro Kemi AB Uppsala Sweden. Melting points, when given, were obtained on a Büchi or a Gallenkamp melting point apparatus and are uncorrected.

Pharmacological tests

The ability of a compound of the invention to bind the $5HT_6$ receptor can be determined using *in vivo* and *in vitro* assays known in the art. The biological activity of compounds prepared in the Examples was tested using different tests.

5-HT_6 Intrinsic Activity Assay

Antagonists at the $5HT_6$ receptor were characterized by measuring inhibition of 5-HT induced increase in cAMP in HEK 293 cells expressing the human 5-HT_6 receptor. Briefly, HEK293/5-HT_6 cells were seeded in polylysine coated 96-well plates at a density of 25 000 / well and grown in DMEM (Dubecco's Modified Eagle Medium) (without phenol-red) containing 5% dialyzed Foetal Bovine Serum for 48h at 37°C in a 5% CO_2 incubator. The medium was then aspirated and replaced by 0.1 ml assay medium (Hanks Balance Salt Solution containing 20 mM HEPES, 1.5 mM isobutylmethylxanthine and 1 mg/ml bovine serum albumin). After addition of test substances, 50 µl dissolved in assay medium, the cells were incubated for 10 min at 37°C in a 5% CO_2 incubator. The medium was again aspirated and the cAMP content was determined using a radioactive cAMP kit (Amersham Pharmacia Biotech, BIOTRAK RPA559). The potency of antagonists was quantified by determining the concentration that caused 50% inhibition of 5-HT (at [5-HT]= 8 times EC_{50}) evoked increase in cAMP, using the formula $Ki=IC_{50}/(1+[5HT]/EC_{50})$.

Method sheet: 96-well displacement assay for 5-HT_6 receptors.

Description for preparation of one plate:

Thaw 1 tube of cells (HEK293-h5-HT6, 0.8-2 mg protein/tube) gently in water bath, temperature lower or equal to 37°C. Add the cells into a polypropylene tube (Falcon) with 8 ml buffer.

Homogenise with a Polytron homogeniser, setting 4, for approximately 10 sec.

Add 2 ml WGA SPA beads (50 mg/ml) and let these couple for 30 min. to the membranes on a rocking platform.

Prepare the assay plates with test compounds and lisuride for NSB, 10 µl of each.

Centrifuge the SPA/membrane mixture at 1000xg for 10 min. Pour out the supernatant and dissolve the pellet in 18.5 ml of buffer.

Immediately before starting the incubation, add [^{3}H]-LSD to the SPA/membrane mixture, final concentration 3 nM.

To each vial add 190 µl of the mixture of membranes, SPA beads and radioligand. Incubate at room temperature for 4 hours before counting in TopCount.

Table 1. Conditions.

Parameter	Setting	Stock concentration	Volume
Buffer	HEPES 20 mM, NaCl 150 mM, $MgCl_2$ 10 mM, EDTA 1 mM, pH 7.4		
Incubation conditions	4 hours room temp.		
Protein	0.8-2 mg/ml (in the tube with cells)		
SPA beads	2 ml/tube	50 mg /ml dH_2O	4 ml
Dilution of SPA-pellet	18.5 ml buffer to 1 tubes with 1 ml cells (0.8-2 mg protein/ml)		20 ml
Radioligand	[^{3}H]-LSD, 3 nM		
NSB	Lisuride, 5 µM	100 µM	10 µl
Test compound		20 times over final	10 µl
Replicates	2, on separate plates		
Assay volume			200 µl

To show the effect of the compounds on food intake the following assay is used:

Method for in vivo assay of reduction of food intake:

Material and methods

Animals

Obese (ob/ob) mouse is selected as the primary animal model for screening as this mutant mouse consumes high amounts of food resulting in a high signal to noise ratio. To further substantiate and compare efficacy data, the effect of the compounds on food consumption is also studied in wild type (C57BL/6J) mice. The amount of food consumed during 15 hours of infusion of compounds is recorded.

Male mice (obese C57BL/6JBom-Lep^{ob} and lean wild-type C57B1/6JBom; Bomholtsgaard, Denmark) 8-9 weeks with an average body weight of 50 g (obese) and 25 g (lean) are used in all the studies. The animals are housed singly in cages at 23±1°C,

12/12-h light/dark cycle is set to lights off at 5 p.m. The animals are conditioned for at least one week before start of study.

Compounds

The test compounds are dissolved in solvents suitable for each specific compound such as cyclodextrin, cyclodextrin/methane sulfonic acid, polyethylene glycol/methane sulfonic acid, saline. Fresh solutions are made for each study. Doses of 30, 50 and 100 mg $kg^{-1}day^{-1}$ are used. The purity of the test compounds is of analytical grade.

Minipump implantation

The animals are weighed at the start of the study and randomized based on body weight. Alzet osmotic minipumps (Model 2001D; infusion rate 8 ul/h) are used and loaded essentially as recommended by the Alzet technical information manual (Alza Scientific Products, 1997; Teeuwes and Yam, 1976). Continuous subcutaneous infusion with 24 hours duration is used. The minipumps are either filled with different concentrations of test compounds dissolved in vehicle or with only vehicle solution and maintained in vehicle pre-warmed to 37°C (approx. 1h). The minipumps are implanted subcutaneously in the neck/back region under short acting anesthesia (metofane/enflurane). This surgical procedure lasts approximately 5 min. It takes about 3 h to reach steady state delivery of the compound.

Food intake measurements

The weight of the food pellets are measured at 5 p.m. and at 8 p. m. for two days before (baseline) and one day after the implantation of the osmotic minipumps. The weigh-in is performed with a computer assisted Mettler Toledo PR 5002 balance. Occasional spillage is corrected for. At the end of the study the animals are killed by neck dislocation and trunk blood sampled for later analysis of plasma drug concentrations.

Determination of plasma concentration

The plasma sample proteins are precipitated with methanol, centrifuged and the supernatant is transferred to HPLC vials and injected into the liquid chromatography /mass spectrometric system. The mass spectrometer is set for electrospray positive ion mode and Multiple Reaction Monitoring (MRM with the transition m/z 316 $\Rightarrow$ 221).

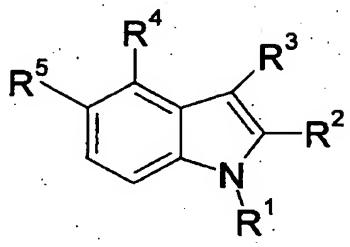
A linear regression analysis of the standards forced through the origin is used to calculate the concentrations of the unknown samples.

Statistical evaluati n

Food consumption for 15 hours is measured for the three consecutive days and the percentage of basal level values is derived for each animal from the day before and after treatment. The values are expressed as mean ± SD and ± SEM from eight animals per dose group. Statistical evaluation is performed by Kruskal-Wallis one-way ANOVA using the per cent basal values. If statistical significance is reached at the level of $p<0.05$, Mann-Whitney U-test for statistical comparison between control and treatment groups is performed.

Claims

1. A compound of the general formula (I):



(I)

in which

R^1 is – SO_2-Ar; -SO_2-alkyl,

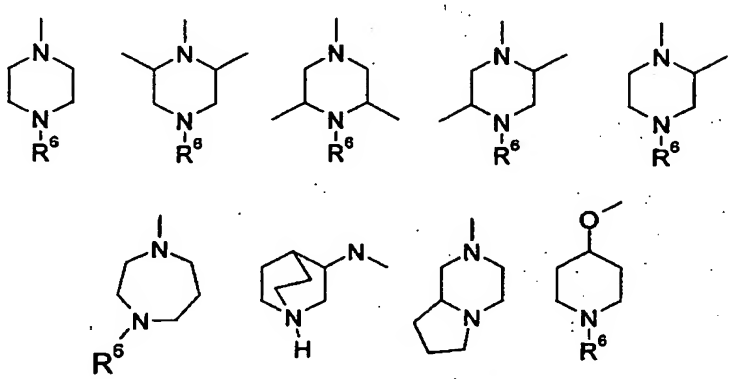
and Ar = phenyl, optionally substituted with F, Cl, Br, C_{1-6} alkyl, CF_3, hydroxy, C_{1-6} alkoxy, OCF_3, amino, alkylamino, dialkylamino, NO_2, methylcarboxyl, aminocarbonyl, SR^7 where R^7 is hydrogen or C_{1-6} alkyl; 1-naphthyl, 2- naphthyl; a bicyclic heterocyclic ring or a 5 to 7-membered partially or completely saturated heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur; and

alkyl = linear or branched C_{1-6} alkyl;

R^2 = H, linear or branched C_{1-4} alkyl;

R^3 = H, 3- [1-azabicyclo[2.2.2]oct-2-en]yl, 3-quinuclidinyl;

R^4 = H, or the following amine groups:



in which R^6 = H or a linear or branched C_{1-6} alkylgroup;

$R^5 = R^4$ or H, hydroxy, C_{1-3}alkoxy, F, NO_2, CF_3, OCF_3;

and pharmaceutically acceptable salts, hydrates, stereoisomeric forms thereof including diastereomers and enantiomers and racemates.

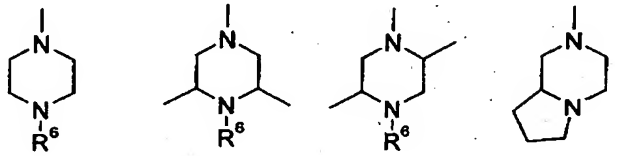
2. A compound according to claim 1, in which

$R^1 = -SO_2$-Ar in which

Ar = phenyl substituted with F or C_{1-6}-alkyl; 1-naphthyl, 2-naphthyl;

R^2 = H, propyl;

R^4 =



R^6 = H

R^5 = H or C_{1-3} alkoxy.

3. A compound according to claim 1, which is

1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,

1-[(4-fluorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole,

1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole,

3-(1-azabicyclo[2.2.2]oct-2-en-3-yl)-1-(phenylsulfonyl)-1H-indole,

5-methoxy-1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,

4-(4-ethyl-1-piperazinyl)-1-(phenylsulfonyl)-1H-indole,

1-[(4-methylphenyl)sulfonyl]-4-(4-methyl-1-piperazinyl)-1H-indole,

1-(phenylsulfonyl)-5-(1-piperazinyl)-1H-indole,

4-(2,5-dimethyl-1-piperazinyl)-1-(phenylsulfonyl)-1H-indole,

4-(2,6-dimethyl-1-piperazinyl)-1-(phenylsulfonyl)-1H-indole,

4-(1,4-diazepan-1-yl)-1-(phenylsulfonyl)-1H-indole,

2-[1-(phenylsulfonyl)-1H-indol-4-yl]octahydropyrrolo[1,2-a]pyrazine1-(2-naphthylsulfonyl)-4-(1-piperazinyl)-1H-indole,

1-(1-naphthylsulfonyl)-4-(1-piperazinyl)-1H-indole,
1-[(4-methylphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole,
N-(1-azabicyclo[2.2.2]oct-3-yl)-N-{1-[(4-methylphenyl)sulfonyl]-1H-indol-4-yl}amine,
2-ethyl-4-(4-ethyl-1-piperazinyl)-1-[(phenyl)sulfonyl]-1H-indole,
2-ethyl-1-(4-methyl-phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,
4-(2,5-dimethyl-1-piperazinyl)-2-ethyl-1-(phenylsulfonyl)-1H-indole,
4-(2,5-dimethyl-1-piperazinyl)-1-[(4-methylphenyl)sulfonyl]-2-propyl-1H-indole,
4-(4-ethyl-1-piperazinyl)-1-[(4-methylphenyl)sulfonyl]-2-propyl-1H-indole,
4-(4-ethyl-1-piperazinyl)-5-fluoro-1-[(4-methylphenyl)sulfonyl]-1H-indole,
5-fluoro-4-(1-piperazinyl)-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1H-indole,
5-chloro-1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,
5-chloro-1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole,
1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-5-methoxy-4-(1-piperazinyl)-1H-indole,
1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-5-(1-piperazinyl)-1H-indole,
1-[(4-methylphenyl)sulfonyl]-4-(3-methyl-1-piperazinyl)-1H-indole,
1-[(4-methylphenyl)sulfonyl]-4-(4-piperidinyloxy)-1H-indole,
1-[(4-methylphenyl)sulfonyl]-4-(3-methyl-1-piperazinyl)-1H-indole.

4. A compound according to claim 3 which is 1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole.

5. A compound according to claim 3 which is 1-[(4-fluorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole.

6. A compound according to claim 3 which is 1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole.

7. A compound according to claims 1 – 6 for use in therapy of a mammal including human being.

8. The compound according to claim 7, wherein the therapy is directed to prophylaxis or treatment of a serotonin-related disease.

9. The compound according to claim 8, wherein the serotonin-related disease is related to the 5-HT_6 receptor.

10. The compound according to claim 9, wherein the disease is obesity.

11. The compound according to claim 9, wherein the disease is a CNS disorder.

12. Use of a compound according to claim1 – 6, for the manufacture of a medicament for treating or preventing a disease related to the serotonin related 5-HT_6 receptor.

13. Use according to claim 12, wherein the disease is obesity.

14. Use according to claim 12, wherein the disease is a CNS disorder.

15. A pharmaceutical composition comprising a compound according to claims 1 – 6 as an active ingredient together with pharmacologically and pharmaceutically acceptable carriers.

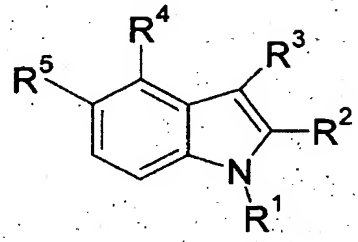
16. A method of treatment or prophylaxis of a disease related to the serotonin related 5-HT_6 receptor in mammals including human beings comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to claims 1 – 6.

17. A method according to claim 16, wherein the disease is obesity.

18. A method according to claim 17, wherein the disease is a CNS disorder.

Abstract

A compound of the general formula (I):



(I)

in which

R^1 is $-SO_2$-Ar; $-SO_2$-alkyl,

and Ar = phenyl, optionally substituted with F, Cl, Br, C_{1-6} alkyl, CF_3, hydroxy, C_{1-6} alkoxy, OCF_3, amino, alkylamino, dialkylamino, NO_2, methylcarboxyl, aminocarbonyl, SR^7 where R^7 is hydrogen or C_{1-6} alkyl; 1-naphthyl, 2- naphthyl; a bicyclic heterocyclic ring or a 5 to 7-membered partially or completely saturated heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur; and

alkyl = linear or branched C_{1-6} alkyl;

R^2 = H, linear or branched C_{1-4} alkyl;

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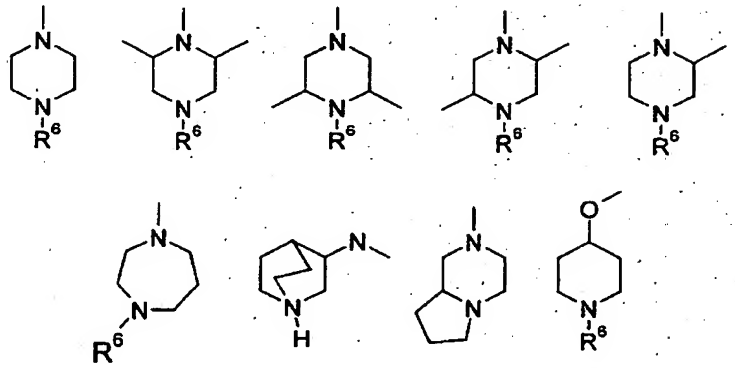

in which R^6 = H or a linear or branched C_{1-6} alkylgroup;

R^5 = R^4 or H, hydroxy, C_{1-3}alkoxy, F, NO_2, CF_3, OCF_3;

and pharmaceutically acceptable salts, hydrates, stereoisomeric forms thereof including diastereomers and enantiomers and racemates.

Further included are pharmaceutical compositions comprising the compounds and the use of the compounds for the preparation of a medicament for the treatment of obesity and CNS disorders as well as method of treatments of these disorders.